UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION **Relates to: ALL CASES**	**MDL No. 13-md-2452-AJB (MDD)** **MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION TO COMPEL PRODUCTION OF CUSTODIAL FILES AGAINST DEFENDANT MERCK SHARP & DOHME CORP.**

Introduction

Plaintiffs seek the production of five additional custodial files from Defendant Merck Sharp & Dohme Corp. ("Merck"). The witnesses are important to issues of general causation and preemption. Merck does not dispute the relevance of these files to Plaintiffs' case. Instead, Merck asserts that producing the custodial files is unnecessary, given the focus of this phase of the litigation.

Merck takes an overly restrictive view of discovery in claiming that Plaintiffs are only entitled to discover scientific data during this phase. Scientific evidence is more than just data, and the additional custodians are important because the data do not tell the full story behind a study. Information about study methodology and data interpretation is often as important as the data itself. "[A]ll studies have 'flaws' in the sense of limitations that add uncertainty about the proper interpretation of the results."[1] Therefore, a study may erroneously result in a finding that there is no association when in fact there is.[2] Details about study methodology, and particularly about Merck's influence on study data, are important to understanding study results and, in turn, important to general causation. The custodial files at issue are very likely

[1] Reference Manual on Scientific Evidence 553 (Fed. Jud. Ctr., 3rd ed. 2011).
[2] *Id.* at 572.

to contain valuable information about study methods and Merck's influence on study data.

Plaintiffs' request is tightly focused. Plaintiffs seek the files of only five Merck employees. Each was involved in designing, producing and/or interpreting study data regarding Januvia and Janumet ("sitagliptin"). Their files are likely to contain information highly relevant to general causation issues. The importance of each employee whose file is sought is summarized below. Upon the Court's request, Plaintiffs will present additional specifics, including internal corporate documents, to the Court for *in camera* inspection. Those materials will help further illustrate the importance of each of the employees to Plaintiffs' case.

A. Brief Summary of Meet and Confer Efforts

Plaintiffs first requested the production of ten additional custodial files from Merck's counsel on July 23, 2014. On July 28, 2014, counsel for Merck asked for the basis for each request in writing. On August 4, 2014, Plaintiffs wrote to Merck's counsel, describing the relevance of each file sought. On August 21, 2014, counsel for both parties participated in a meet-and-confer conference call. During the call, Plaintiffs asked Merck's counsel to identify the bases for their objection to each custodian whose file Merck refused to produce. Instead of identifying specific objections, counsel for Merck asserted generally that additional productions were not appropriate, but agreed to produce the files of three custodians of Plaintiffs' choosing.[3] On August 26, 2014, Plaintiffs offered to accept five of the ten custodial files requested. On August 28, 2014, Merck's counsel refused to produce five files.

[3] Merck reversed course from its initial response. On August 4, Merck requested the basis for each of Plaintiffs' requests. On August 21, Merck claimed that Plaintiffs were not entitled to any further custodial files during this phase of the case, regardless of the basis for Plaintiffs' requests.

B. Description of the Discovery Sought to be Compelled

The five custodial files Plaintiffs request from Merck, and the bases for Plaintiffs' requests, are as follows:

1. Cynthia Girman

Cynthia Girman is an epidemiologist and biostatistician who extensively studied the post-marketing effects of sitigliptin. She is an Executive Director at Merck and the head of the Data Analytics and Observational Methods unit in the Center for Observational and Real World Evidence. Dr. Girman is also a core member of the Risk Management Safety Team at Merck. She often presented on possible epidemiology collaborations in front of Merck's Safety Review Committee. She has also published epidemiology studies about sitagliptin.

Dr. Girman studied at the University of North Carolina and worked actively with UNC staff on pharmacoepidemiology methods, including study design and analysis. Her colleagues at UNC, including endocrinologist Dr. John Buse and epidemiologist Til Sturmer, proposed to collaborate with Merck on a pancreatic cancer epidemiology study. Specifically, Dr. Buse and company proposed to design a study to combat a study by Dr. Michael Elashoff that found an increased risk of pancreatic cancer in patients on Januvia, compared with other anti-diabetic therapies.[4] Dr. Buse is a member of Amylin's Advisory Board who has a history of aggressively inundating the medical literature with publications backing the safety of the incretin mimetics.[5] In 2009, Dr. Buse orchestrated a closed door meeting with representatives

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[4] The Elashoff study was discussed by the parties at Science Day. It showed a 2.7 fold increased risk for pancreatic cancer in users of Januvia, compared with other diabetic therapies. Elashoff M, Matvyenko AV, Gier B, Elashoff R, Butler PC. *Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies.* Gastroenterology 2011:141(1):150-6.

[5] Plaintiffs are scheduled to take the Third Party deposition of Dr. Buse on September 23, 2014 in Chapel Hill, North Carolina.

of some of the Defendants and members of the FDA, including Amy Egan. The stated goal of the "closed door, by invitation only" meeting was to write a joint manuscript that presumably would carry forward the drug manufacturers' objectives, with the blessings of the FDA officials in attendance.

When Dr. Buse, Dr. Sturmer, and other UNC doctors presented their study proposal to Merck, Dr. Girman applauded their proposed methodological approach and promoted the proposal to Merck. Ultimately, the study moved forward with input from Merck about the study protocol and methodology, and not surprisingly, the conclusions contradicted the results of the Elashoff study.

Dr. Girman appears to have significant influence over study design and methodology as an epidemiologist at Merck. Plaintiffs expect Dr. Girman's custodial files to reveal more information about her involvement in this study and others similar to it. This background information provides important context about Merck's studies that is simply not available from looking only at data.

2. Kim Brodovicz

Kim Brodovicz is also an epidemiologist at Merck. She is a Senior Principal Scientist in Epidemiology, a position she has held since 2012. Previously, she was an Associate Director of Epidemiology. She began working in Epidemiology at Merck in 1997. Dr. Brodovicz did extensive work looking at the methodological issues in studying pancreatic cancer. She presented on the topic and was involved in determining whether databases such as CPRD, MarketScan, and SEER were sufficient to study pancreatic cancer. It is important for Plaintiffs to examine the results of these efforts and her thoughts on whether these databases were appropriate to study pancreatic cancer and sigtagliptin use.

Dr. Brodvicz was also the epidemiology representative on Merck's Risk Management Safety Team. She presented draft Epidemiology protocols and took suggestions. She has published on the pancreatic cancer risks of Type-2 Diabetics and the pancreatic safety of GLP-1 based drugs.

Like Dr. Girman, Dr. Brodovicz appears influential in study design and methodology. Documents show that she is responsible for analyzing study methodology for the Risk Management Safety Team, specifically for studies of pancreatic cancer.

3. Harvey Katzeff

Harvey Katzeff is the Global Executive Director of Scientific Affairs in the Diabetes Group at Merck. He was often contacted by external investigators with research proposals. Dr. Katzeff set up and led a consortium of pancreatic experts who gave their opinions related to pancreatic cancer. On May 17, 2013, Dr. Katzeff organized a Scientific Input Engagement meeting on pancreatic cancer, with various external researchers.

Plaintiffs believe Dr. Katzeff also met with independent researchers to discuss data generated by using competitor drugs in animals. For example, it appears that he met with Dr. Franco Folli, who conducted a study on baboons. Dr. Folli offered to share the Byetta data with Merck confidentially at an American Diabetes Association meeting. Dr. Katzeff appears to have set up a meeting with Dr. Folli and Nancy Thornberry (discussed below) to review the data and protocol, with the idea being that there may be a future collaboration to study Januvia.

4. Nancy Thornberry

Dr. Thornberry worked at Merck from 1979 until July, 2013. She is a biochemist by trade. She left Merck as the Senior Vice President and Franchise Head of the Diabetes and Endocrinology department. Previously, she was the Senior Vice President and Franchise Head of the Diabetes and Obesity department. Dr. Thornberry led a group of biochemists and molecular biologists who initiated the discovery of Januvia, and she was involved in all aspects of developing Januvia. She was heavily involved in the Pancreas Scientific Input Engagement with key opinion leaders; she liaised with experts in the field; and she was frequently included on e-mails discussing high-level science. Dr. Thornberry is likely the most knowledgeable

person at Merck on Januvia, and Plaintiffs are surprised she was not mentioned by Merck as one of the initial custodians.

5. Bei Zhang

This Court heard about the work of Dr. Peter Butler at the Larry Hillblom Islet Research Center at UCLA. Dr. Butler found worrisome changes in the pancreases of rats, and later in humans who had used incretin mimetics. Although Defendants now criticize Dr. Butler's work, his research began at the behest of Merck, when Merck engaged Dr. Butler's team to investigate the properties of sitigliptin. Merck negotiated a study protocol and negotiated the choice of lab animal, the transgenic HIP rat. However, when the work produced unwanted effects in the rats, Merck disassociated itself from UCLA.

This story line again demonstrates Merck's influence on studies, and ultimately study data. Plaintiffs initially requested the file of George Lankas, who was in charge of many of the pre-approval animal studies for sitigliptin, to better understand the animal results. Plaintiffs now seek the file of Bei Zhang in place of Dr. Lankas, after discovering that Dr. Lankas left Merck shortly after Januvia's marketing approval.[6] Dr. Zhang was one of Dr. Butler's main contacts at Merck, and Plaintiffs believe she traveled to visit Dr. Butler at UCLA. On February 29, 2008, Dr. Butler wrote Dr. Zhang and another Merck employee to inform them that, during an independent study, a rat treated with Januvia developed pancreatitis. Further, he informed Dr. Zhang that Januvia-treated animals had greater pancreatic weight, increased cell replication and decrease cell apoptosis (cell death), which could increase the risk of pancreatic cancer. These mechanisms are a key component to Plaintiffs' general causation arguments. Specifically, they help explain the biological plausibility of how sitigliptin causes pancreatic cancer.

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[6] George Lankas left the company in 2006. Dr. Zhang's employment appears to span from 2001 to 2010.

These facts raise important questions that Dr. Zhang's custodial file should help to answer. What did Dr. Zhang and other animal researchers at Merck do with this information from Dr. Butler? Did they recognize the harmful effects of the drug? Did she and others at Merck responsible for animal studies collaborate with other researchers to try to explain them away in other studies? Dr. Zhang was contacted by other researchers, such as Dr. Daniel Drucker, who often conducted animal studies funded by industry, and she spoke out against Dr. Butler's work. Dr. Zhang also served as a reviewer on the Merck committee that evaluated Investigator Initiated Studies. In this capacity, she had an important role in deciding what studies the company would allow to proceed.[7]

Plaintiffs should be allowed to review the decision-making process as to which studies went forward and which potential studies did not. These facts shed light on the credibility of the study data actually generated. In addition, Plaintiffs reasonably expect that Dr. Zhang's file would include information about studies or study data that was never reported to the FDA.

C. Discovery Sought is Primarily Related to General Causation Issues

Plaintiffs request these five custodians because of their importance to general causation. Some of the files also have relevance to preemption. Each of these files likely will contain important information about Merck's studies of sitagliptin, including reasons for the studies, interpretation of data, and study designs. What Plaintiffs have now is the data reported by the company and data reported in the open literature. Some of these custodial files potentially would show studies and data not reported to the FDA. They could show the science available to Merck against the much more limited science Merck shared with the FDA.

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[7] Independent studies with Januvia, like many other pharmaceutical products, cannot be conducted unless researchers can obtain drug product directly from the company. As such, it is important to determine whether Merck was preventing certain types of studies from going forward.

D. Relevance and Necessity of the Requested Discovery

Merck has only produced eight custodial files to date. Eight files were contemplated as an **initial** production, pursuant to this Court's Order Governing the Production of Electronically Stored Information. (Dkt. No. 187). Upon substantial completion of this initial production of custodial files, the Parties were to meet and confer concerning the production of **additional** custodial files. (*Id.* at 6). Despite this order, Merck has now shunned Plaintiffs' requests and taken the position that Plaintiffs are not entitled to any additional custodial files.

Plaintiffs are entitled to the five custodial files they are now requesting. Fed. R. Civ. P. 26(b)(1) permits parties to "obtain discovery regarding any non-privileged matter that is relevant to any party's claim or defense -- including the existence, description, nature, custody, condition, and location of any documents or other tangible things and the identity and location of persons who know of any discoverable matter." Further, "[r]elevant information need not be admissible at the trial if the discovery appears reasonably calculated to lead to the discovery of admissible evidence." *Id.* The files requested by Plaintiffs are discoverable, and Merck has not disputed their relevance. In fact, Merck has not offered any objection to any of the individual custodians Plaintiffs have requested.

Currently, Plaintiffs are missing critical information. Merck has produced **no files** from epidemiologists. The files from Drs. Girman and Brodovicz would be the first. Plaintiffs have been unable to locate any raw data, draft papers or proposed protocols for any of the proposed or completed studies. As authors of, and integral figures in, such studies, Dr. Girman and Dr. Brodovicz likely have this information in their files. Plaintiffs are also missing the file of the scientific founder of Januvia, Nancy Thornberry. And, no files so far contain information surrounding the discussions that Drs. Katzeff and Zhang had with key external researchers.

Without these files, Plaintiffs are handicapped in assessing the reliability of the very data Merck will use to cross-examine Plaintiffs' experts. The requested files

relate to individuals whose titles alone indicate involvement with critical information regarding the safety of Januvia and Janumet. Their files likely include information critical to Plaintiffs' case. They were key players in moving the science forward on behalf of Merck. They were also at the heart of the corporate discussions about these drugs, including their development, their pancreatic cancer risks, and the management of those risks via study design.

When study data and literature are evaluated, it is important to consider whether the research was independent, or whether it was financed, underwritten and influenced by the drug sponsor. Defendants have driven the science on these drugs. Plaintiffs have the right to discover whether this science, by design, overlooked or trivialized the pancreatic cancer risk.

Merck would like Plaintiffs and the Court to simply accept its data without questioning its methods. This lack of transparency defies the scientific method and prevents Plaintiffs and their experts from assessing the credibility of the data. For the parties and the Court to objectively assess the causation issue, the strengths and weaknesses of the scientific data must be evaluated. The custodians at issue, who have been working with sitagliptin for years, have knowledge about the strengths and weaknesses of the data. They spent countless hours actually researching their research methods. Those methods dictated the data ultimately generated when studying pancreatic cancer. Plaintiffs should have the right to analyze that process to appropriately weigh the study data.

The burden on Merck to produce these five files is minimal compared to other cases and compared to the value of the files in this case. Typically in an MDL like this, it is not uncommon for a Defendant to produce fifty or more custodial files of corporate witnesses. Plaintiffs understand that not all custodial files should be produced during this phase of this litigation, but Plaintiffs have gone to great pains to narrowly tailor their requests. Although the focus should be on the discoverability of the files, it is noteworthy that the number of files Plaintiffs are requesting is minimal.

If Plaintiff's motion is granted, Merck will still only have produced a total of thirteen custodial files.

Plaintiffs are willing to provide further details about the importance of these files, but are hesitant to divulge their work product to Defendants. Plaintiffs welcome the opportunity to present further evidence for the Court's *in camera* inspection if the Court deems it necessary.[8]

Conclusion

For the foregoing reasons, Plaintiffs respectfully request this Court to order Merck to produce the custodial files of Cynthia Girman, Kim Brodovicz, Harvey Katzeff, Nancy Thornberry and Bei Zhang, per the Court's Order Governing the Production of Electronically Stored Information entered November 15, 2013. (Dkt. No. 187).

DATED: September 8, 2014

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[8] *See Save v. County of Santa Clara*, 2004 WL 2695606 at *1 (N.D. Cal. Jan. 21, 2004) (finding no prejudice to opposing party in granting *in camera* inspection to prevent disclosure of privileged documents); *Roberts v. Norris*, 526 F. Supp. 2d 926, 945-46 (E.D. Ark. 2007) (granting request for counsel affidavit to be considered ex parte and *in camera* in order to protect the attorney-client privilege and the work-product privilege).

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CERTIFICATE OF SERVICE

I hereby certify that on September 8, 2014, I caused the above document to be filed via the CM/ECF system for the Southern District of California, and the CM/ECF system served the same upon all registered users at their registered email addresses.

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